

### **REMARKS**

Claims 4-11 are pending in the instant application. Claim 4 has been amended. The amendment to claim 4 adds no new matter. Applicants respectfully reserve the right to pursue subject matter given up with this amendment at a later date. Applicants gratefully acknowledge the Examiner's removal of the finality of the previous Office Action pursuant to Applicant's filing of a request for continued examination under 37 CFR 1.114.

#### **Double Patenting**

Claims 4-11 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/291,058.

In response, Applicants note that such a provisional obviousness-type double patenting rejection should eventually, when it is the only rejection remaining in an application, be withdrawn by the Examiner so as to permit the application to issue as a patent. At such time the provisional obviousness-type double patenting rejection in the other application should be converted into a nonprovisional obviousness-type double patenting rejection (see MPEP §804 (I)(B)).

Accordingly, Applicants respectfully request that the instant provisional obviousness-type double patenting rejection be held in abeyance until a finding of allowable subject matter has been made in one of the cited applications. At such time the provisional obviousness-type double patenting should be removed in that application, and a nonprovisional obviousness-type double patenting rejection may be made in the remaining application. Then the scope of the allowed claims can be compared to the scope of the pending claims in the remaining application, and a proper assessment of the obviousness issue, under the judicially-created doctrine of obviousness-type double patenting, can be made.

#### **Rejection under 35 U.S.C. §103**

The Office Action states that claims 4-6 continue to be rejected under 35 U.S.C. §103(a) as being unpatentable over Metelev *et al.* (U.S. Patent No. 6,143,881) in combination with Ghosh *et al.* ((1993) Anti-Cancer Drug Design 8(1): 15-32). The Office Action further states

that claims new claims 7-11 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over the same combination of references. In particular, the Office Action states that “one of ordinary skill in the art would have been motivated to combine the phosphorothioate-phosphodiester oligonucleotide co-polymer design taught by Ghosh *et al.* into the hybrid oligonucleotide taught by Metelev *et al.* to obtain the benefits of antisense design taught by each Ghosh *et al.* and Metelev *et al.*” Applicants respectfully traverse this rejection for the reasons that follow.

First, Applicants have asserted, and continue to assert, that no specific motivation to combine the Metlev *et al.* and the Ghosh *et al.* references has been presented. On this point, the Office Action states that “both Ghosh *et al.* and Metelev *et al.* teach their modification for the purpose of creating an improved antisense molecule” and that, therefore, no showing of a motivation to combine is necessary. In support of this proposition, the Office Action relies upon a part of the holding in *In re Kerkhoven*, which states that “it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to used for the very same purpose” (*In re Kerkhoven*, 626 F.2d 846 (CCPA 1980)).

However, Applicants respectfully submit that the cited language from the holding in *Kerkhoven* is not controlling here, and, further, that the teaching of separate “improvements” does not, in any case, provide the level of specificity to support a *prima facie* case for obviousness. A proper inquiry into obviousness is highly factual and is based upon the knowledge and understanding of one of skill in the art (see *Graham v. John Deere Co.* 383 U.S. 1 (1966)). Accordingly, the technical features of the claimed invention and the particular technical field involved necessarily weigh heavily in the determination and it would be clearly improper to blindly apply the language of part of an obviousness holding in one technical field to that of an obviousness rejection in another, absent a considered application of the particular facts in each case.

Indeed, the facts in the *In re Kerkhoven* case are eminently distinguishable from those in the instant application. In *Kerkhoven*, the technology was a method of preparing a detergent mixture with two different detergent compositions, each of which was separately described in the prior art. Accordingly, the field of art in *Kerkhoven* related to chemical detergents, a field that is

much simpler and more predictable than the field of Applicant's invention, which relates to biologically active antisense oligonucleotides that act *in vivo* on specific biological targets.

In Applicant's invention, the supposedly common "same purpose" of Metlev *et al.* and Ghosh *et al.* asserted by the Examiner is an "improved antisense molecule." However, Applicants respectfully assert that an "improvement" cannot be considered a specific "purpose" under the cited legal test provided by *Kerkhoven*. If an "improvement" were to be considered, in all cases, a specific "purpose" as provided in *Kerkhoven*, then the need to specifically demonstrate a motivation to combine two references teaching individual "modifications" to render a claimed combination of such modifications obvious under 35 U.S.C. §103 would be virtually eliminated. This so because almost all reportings of "modifications" reported in a specific technical body of literature could, at some level, be characterized as individual "improvements" that therefore might "obviously" be combined. The safeguards against hindsight-based applications of 35 U.S.C. §103 would, therefore, be lost if a mere "improvement" was the standard for defining a common purpose under the *Kerkhoven* decision.

In this case, the Metlev *et al.* and Ghosh *et al.* references do not teach individual modifications for the same purpose. In particular, the Metlev *et al.* reference is relied upon for teaching 2'-OMe modifications that increase duplex stability, while Ghosh *et al.* is relied upon for teaching phosphorothioate-phosphodiester oligonucleotide co-polymers, which provide a reasonable level of nuclease resistance. Indeed, the Examiner has stated on the record that "the properties of Ghosh *et al.* oligos and the Metlev *et al.* oligos dovetail" (emphasis added, page 5, final line to page 6, line 1 of the Office Action dated August 26, 2003). Applicants respectfully assert that two such teachings which "dovetail" cannot be said to provide a common purpose under *Kerkhoven* because, as the term "dovetail" suggests, different, albeit complementary, functions are being supplied by each reference. Therefore, Applicant asserts that no *prima facie* case for obviousness has been presented because there is no true common purpose for the separate modifications taught by Ghosh *et al.* and Metlev *et al.* and, still further, there is no motivation to combine these two teachings to arrive at the instant claimed invention.

Further on the lack of a motivation to combine the cited references, Applicants respectfully note that one of the inventors in the instant application (Dr. Sudhir Agrawal) was also a primary inventor on the Metlev *et al.* patent cited by the Examiner in this rejection. Accordingly, at the time of the Metlev *et al.* patent, Dr. Agrawal had actual prior knowledge of

the cited prior art teachings, but did not consider claiming the mixed-modified oligonucleotides of the instant invention until his later work with another confirmed the benefits of the claimed combination. This, in itself, is strong circumstantial evidence for the lack of obviousness to the skilled artisan of the instantly claimed invention.

Second, Applicants further assert that no *prima facie* case for obviousness has been presented because there was also no reasonable expectation of success of combining the cited art at the time of the invention. It is well established law that a proposed modification or combination of prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991) (where the idea of using a monkey gene to probe for a homologous human gene may have been “obvious to try,” but was not obvious under 35 U.S.C. §103 because many pitfalls existed that would have precluded a “reasonable expectation of success.”).

The relevant literature in this field is replete with evidence that combining two or more independent oligonucleotide modifications, known in the art, has unpredictable consequences for the resulting mixed-modification oligonucleotide. Therefore, even accepting the logic of the rejection that the instant invention is an “obvious” combination of elements taught by different references, nevertheless a reasonable expectation of success was lacking at the time of the invention and so the claimed combination is not obvious under 35 U.S.C. §103. Applicants assert that the unpredictability of combining different types of antisense oligonucleotide chemical modifications has not been acknowledged. Indeed, while Applicants have submitted evidence of the unexpected results obtained with their own mixed-modification oligonucleotide, this evidence has been largely ignored.

In summary, Applicants respectfully assert that the quoted language from the holding in *In re Kerkhoven* is not controlling here, because the facts in that case are so factually remote from those in the instant application and, in any event, there was no reasonable expectation of success even if the claimed combination of modifications was obvious to try.

Further on this point, Applicant’s last Response included evidence, in the form of experimental data, showing that a member of the claimed class of hybrid oligonucleotides has unexpected properties that would, in any event, rebut the case presented for obviousness. In response, the instant Office Action states that Applicant’s submission of evidence is “not found

to be persuasive because one oligonucleotide with unexpected results is not sufficient to demonstrate unexpected results for the many different types of oligonucleotides encompassed in the claims...(and that)....these unexpected result do not address the scope of the claims” (emphasis added).

Not in acquiescence to the Examiner’s rejection and, further, notwithstanding Applicant’s continued assertion that the claimed invention is not *prima facie* obvious, Applicants have amended claim 4 to narrow the subject matter claimed so as to facilitate the timely prosecution of this application. In particular, Applicants have narrowed claim 4 to require that the claimed oligonucleotides include one or more segments of 2’-O-substituted ribonucleotides that are linked by phosphodiester or phosphorothioate internucleoside linkages. While, Applicants respectfully reserve the right to pursue subject matter given up with this amendment, the amendment effectively narrows the claimed class so that that the experimental evidence of unexpected results proffered in their last response is commensurate with the breadth of the claimed subject matter.

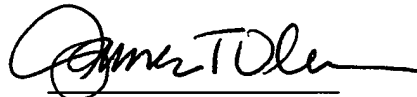
Accordingly, reconsideration and withdrawal of the rejection is respectfully requested in view of this narrowing amendment and the arguments presented above.

**CONCLUSION**

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

The time for responding to this action has been extended to December 12, 2004 by the accompanying Petition for a One Month Extension of Time and payment of fee. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



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